Integrated Two-Analyte Population Pharmacokinetic Model of Polatuzumab Vedotin in Patients with Non-Hodgkin Lymphoma

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Supplementary Information

NONMEM code for the final model is shown below:

```
$SUBROUTINES ADVAN13 TRANS1 TOL=11
$MODEL
COMP=(central)
COMP=(peri)
COMP=(mmae)
COMP=(mmae)
$PK
BCEL = 1
IF(BBCC.GT.THETA(36)) BCEL=BBCC/THETA(36)
BCEL1 = 1
IF(BBCC.GT.1) BCEL1=BBCC
RTX = 0
IF(COMBO.EQ.1) RTX = 1
GA101 = 0
IF(COMBO.EQ.2) GA101 = 1
SEX = SEXN - 1
NAIVE = 0
IF(RRFN.EQ.0) NAIVE=1
ASIAN = 0
IF(RACEN.EQ.1) ASIAN = 1
HEPA = 0
IF(BHPTGRPN.GT.1.5.AND.BHPTGRPN.NE.9999) HEPA = 1
ECOG0 = 0
IF(BECOG.EQ.0) ECOG0 = 1
ECOG2 = 0
IF(BECOG.EQ.2) ECOG2 = 1
COVV1 = THETA(24)**SEX*THETA(25)**ASIAN*THETA(26)**NAIVE
```

```
COVCLINF =
THETA(27)**SEX*(BALBUM/35)**THETA(28)*THETA(29)**(RTX+GA101)*BCEL1**THETA(30)*(1+THE
TA(31)*(BTMBD/5000-1))
COVKDES = THETA(32)**NAIVE*THETA(33)**(RTX+GA101)
COVCLT = THETA(34)**NAIVE*BTMBD/(THETA(35)+BTMBD)*BCEL**THETA(37)
KDES = THETA(1)*COVKDES
CLT = THETA(2)*COVCLT*EXP(ETA(1))
CLINF = THETA(3)*(BWT/75)**THETA(22)*COVCLINF*EXP(ETA(2))
V1 = THETA(4)*(BWT/75)**THETA(23)*COVV1*EXP(ETA(3))
V2 = THETA(5)*(BWT/75)**THETA(23)*EXP(ETA(4))
Q = THETA(6)*(BWT/75)**THETA(23)*EXP(ETA(5))
VMAX = THETA(7)*EXP(ETA(6))
KM = THETA(8)
CLINFEMAX= THETA(9)
T50 = THETA(10)*24*30
GAM = THETA(11)
T50GAM = T50**GAM
S1 = V1
; Re-parameterization
K12 = Q/V1
K21 = Q/V2
; MMAE part
COVMMAE1=
(BWT/75)**THETA(38)*THETA(39)**SEX*THETA(40)**NAIVE*THETA(41)**(RTX+GA101)*THETA(42)
**HEPA
COVMMAE = COVMMAE1*THETA(43)**ECOG0*(BALBUM/35)**THETA(44)
FRAC0 = COVMMAE*EXP(ETA(7))
VMMAE = THETA(12)
CLMMAE = THETA(13)*EXP(ETA(8))
QMMAE = THETA(14)
V2MMAE = THETA(15)*EXP(ETA(9))
VMAXMMAE = THETA(16)
KSS = THETA(17)
FRAC1 = THETA(18)
```

```
FRAC2 = THETA(19)
ALPH = THETA(20)/24/30
FREMAX = THETA(21)
K34 = QMMAE/VMMAE
K43 = QMMAE/V2MMAE
K30 = CLMMAE/VMMAE
$DES
FRAC = FRAC0*(1+FREMAX*EXP(-ALPH*T))
TGAM = 0
IF(T.GT.0) TGAM = T**GAM
CL=CLT*EXP(-KDES*T)+CLINF*(1+CLINFEMAX*T50GAM/(T50GAM+TGAM))
K10 = CL/V1
KINPUT = FRAC*(FRAC1*CLT*EXP(-
KDES*T)/V1+CLINF*(1+CLINFEMAX*T50GAM/(T50GAM+TGAM))/V1+FRAC2*VMAX/(KM+A(1)/V1))
DADT(1)= K21*A(2)-K12*A(1)-K10*A(1)-VMAX*A(1)/(KM+A(1)/V1)
DADT(2)=-K21*A(2)+K12*A(1)
DADT(3)= KINPUT*A(1)-K30*A(3) - K34*A(3) + K43*A(4) - VMAXMMAE*A(3)/(KSS+A(3)/VMMAE)
DADT(4)= K34*A(3) - K43*A(4)
$ERROR
ACMMAE = A(1)/V1
MMAE = A(3)/VMMAE
TY=ACMMAE
IF (TYPE.EQ.6) TY=MMAE
Y=TY*(1+EPS(1)*EXP(ETA(10)))
IF (TYPE.EQ.6) Y=TY*(1+EPS(2)*EXP(ETA(11)))
W = SQRT(SIGMA(1,1))*TY*EXP(ETA(10))
IF (TYPE.EQ.6) W = SQRT(SIGMA(2,2))*TY*EXP(ETA(11))
IRES = DV-TY
IWRES = IRES/W
IPRED = Y
```

Equations for the final model are shown below:

Equations:

$dA_1/dt = -K_{10} A_1 - K_{12} A_1 + K_{21} A_2 - V_{MAX} A_1/(K_M + A_1/V_1)$;

$dA_2/dt = -K_{12} A_1 - K_{21} A_2$;

$dA_3/dt = K_{INPUT} A_1 - K_{30} A_3 - K_{34} A_3 + K_{43} A_4 - V_{MAX,MMAE} A_3/(K_{SS}+A_3/V_{MMAE})$;

$dA_4/dt = K_{34} A_3 - K_{43} A_4$.

Notations:

$FRAC = FRAC_0 (1+FRAC_T e^{-\alpha \cdot t})$; $CL_T=CL_{T0} e^{-Kdes \cdot t}$; $CL_{NS}=CL_{INF} \cdot (1+CL_{INF,EMAX} T_{50d}^{\gamma} / (T_{50d}^{\gamma} + t^{\gamma}))$;

$CL_{MM}= V_{MAX} V_1/(K_M + A_1/V_1)$; $CL = CL_T+CL_{NS}$; $K_{10} = CL/V_1$;

$K_{INPUT} = FRAC (CL_{NS} + FRAC_{CLT} CL_T + FRAC_{MM} CL_{MM})/V_1$;

$K_{12} = Q/V_1$; $K_{21} = Q/V_2$; $K_{34} = Q_{MMAE}/V_{MMAE}$; $K_{43} = Q_{MMAE}/V_{2,MMAE}$; $K_{30} = CL_{MMAE}/V_{MMAE}$;

$T_{50d} = T_{50}*24*30$; $\alpha = ALPH/24/30$; $K_{DES} = \theta_1 \cdot COV_{KDES}$

Random Effects Model:

$CL_{T0} = \theta_2 \cdot COV_{CLT} \cdot e^{\eta 1}$; $CL_{INF} = \theta_3 \cdot COV_{CLINF} \cdot e^{\eta 2}$; $V_1 = \theta_4 \cdot COV_{V1} \cdot e^{\eta 3}$;

$V_2 = \theta_5 COV_{V2} \cdot e^{\eta 4}$; $Q = \theta_6 \cdot COV_Q \cdot e^{\eta 5}$; $V_{MAX} = \theta_7 \cdot e^{\eta 6}$; $FRAC_0 = COV_{MMAE} \cdot e^{\eta 7}$;

$CL_{MMAE} = \theta_{13} \cdot e^{\eta 8}$; $V_{2,MMAE} = \theta_{15} \cdot e^{\eta 9}$; $\eta_i=N(0,\omega_i^2)$, i = 1, ..., 9.

Covariate Model:

COV_{CLT} = [θ_{34} if treatment-naive]·TMBD/(θ_{35}+TMBD)·max(1,Bcell/θ_{36})$^{\theta 37}$;

COV_{KDES} = [θ_{32} if treatment-naive]·[θ_{33} if with rituximab or obinutuzumab];

COV_{CLINF} = (WT/75)$^{\theta 22}$·[θ_{27} if male]*(ALBUM/35)$^{\theta 28}$·[θ_{29} if with rituximab or obinutuzumab]·
max(1,Bcell)$^{\theta 30}$·[1+ θ_{31}(TMBD/5000-1)];

COV_{V1} = (WT/75)$^{\theta 23}$·[θ_{24} if male]·[θ_{25} if Asian]·[θ_{26} if treatment-naive];

$COV_{V2} = COV_Q$ = (WT/75)$^{\theta 23}$;

COV_{MMAE} = (WT/75)$^{\theta 38}$·[θ_{39} if male]·[θ_{40} if treatment-naive]·[θ_{41} if with rituximab or obinutuzumab]·
[θ_{42} if hepatic impairment]·[θ_{43} if EC0G=0]·(ALBUM/35)$^{\theta 44}$.

Residual Error Model:

$acMMAE_{IPRED} = A_1/V_1$; $acMMAE_{observed} = acMMAE_{IPRED} \cdot (1+\varepsilon_1 \cdot e^{\eta 10})$;.

$MMAE_{IPRED} = A_3/V_{MMAE}$; $MMAE_{observed} = MMAE_{IPRED} \cdot (1+\varepsilon_2 \cdot e^{\eta 11})$;

(η_{10}, η_{11}) =MVN(mean=diag(0,0),var=c($\omega_{10,10}$,$\omega_{10,11}$;$\omega_{10,11}$,$\omega_{11,11}$)); $\varepsilon_1=N(0,\sigma_1^2)$; $\varepsilon_2=N(0,\sigma_2^2)$.

Parameter estimates:

Parameter values can be found in Table 2 and Table S3.

Table S1 Clinical trials of polatuzumab vedotin included in the population PK analysis

Study	Phase	Patients	Treatment	PK sampling timepoints	References
DCS4968g (NCT01290549)	I/Ib	R/R B-cell NHL or CLL (*n* = 95)	**Phase I single agent** Pola: 0.1, 0.25, 0.5, 1.0, 1.8, or 2.4 mg/kg Q3W	C1D1 0, 0.5, 4, and 24hr, C1D4, C1D8, C1D11, C1D15, C2D1 0, 0.5, and 4hr, C2D8, C2D15, C3–4D1 0 and 0.5hr, C3–4 D8, D15, C5–8D1 0 and 0.5hr, C8D15, C12, and every 4th cycle beyond 0 and 0.5hr, TC/ET + PT	Palanca-Wessels *et al.* 2015[1]
			Phase Ib combined with rituximab R: 375 mg/m^2 Pola: 2.4 mg/kg Q3W	C1D2 0 and 0.5hr, C1D4, C1D8, C1D15, C2–4D2 0 and 0.5hr, C2–4D8, C2–4 D15, C5–8, C12, and every 4th cycle after, D2 0 and 0.5hr, TC/ET + PT	
GO27834 (NCT01691898, ROMULUS)[a]	Ib/II	R/R B-cell NHL (DLBCL or FL) (*n* = 142)	**Phase Ib safety run in** G: 1,000 mg Pola: 1.8 mg/kg Q3W	C1D2 0 and 0.5hr, C1D8, C1D15, C2D1 0 and 0.5hr, C4D1 0 and 0.5hr, TC/ET + PT	Morschhauser *et al.* 2019;[2] Phillips *et al.* 2016[3]
			Phase II R: 375 mg/m^2 Pola: 2.4 mg/kg Q3W	C1D2 0 and 0.5hr, C1D8, C1D15, C2D2, C3D2 0 and 0.5hr, C3D8, C3D15, C4D2 0 and 0.5hr, and every 4th cycle after, TC/ET + PT	

			R: 375 mg/m^2 Pola: 1.8 mg/kg Q3W		
			Phase II expansion G: 1,000 mg Pola: 1.8 mg/kg Q3W	C1D2 0 and 0.5hr, C1D8, C1D15, C2D1 0 and 0.5hr, C4D1 0 and 0.5hr, TC/ET + PT	
GO29365 (NCT02257567)[b]	Ib/II	R/R FL or DLBCL (*n* = 106)	**Phase Ib safety run in** B: 90 mg/m^2 R: 375 mg/m^2 Pola: 1.8 mg/kg Q3W (DLBCL) or Q4W (FL) B: 90 mg/m^2 G: 1,000 mg Pola: 1.8 mg/kg Q3W (DLBCL) or Q4W (FL)	**Phase Ib safety run in** C1D2 0 and 0.5 hr, C1D8, C1D15, C2D1, C4D1 0 and 0.5 hr	Matasar *et al.* 2017;[4] Matasar *et al.* 2017[5]
			Phase II randomization B: 90 mg/m^2 R: 375 mg/m^2	C1D2 0 and 0.5 hr, C2D1 0 hr, C4D1 0 and 0.5 hr, TC	

			Pola: 1.8 mg/kg Q3W (DLBCL) or Q4W (FL) B: 90 mg/m^2 R: 375 mg/m^2		
			Phase II expansion B: 90 mg/m^2 G: 1,000 mg Pola: 1.8 mg/kg Q3W (DLBCL) or Q4W (FL)	C1D2 0 and 0.5 hr, C2D1 0 hr, C4D1 0 and 0.5 hr, TC	
GO29044 (NCT01992653)[c]	Ib/II	Previously untreated DLBCL (*n* = 45)	**Phase Ib dose escalation** R 375 mg/m^2 Cyclophosphamide: 750 mg/m^2 Doxorubicin: 50 mg/m^2 Pola: 1.0, 1.4, 1.8, or 2.4 mg/kg Q3W	C1D2 0 and 0.5hr, C1D8, C1D15, C2D2, C3D1, C4D1 0 and 0.5hr, PT	Tilly *et al.* 2019[6]

			G: 1,000 mg Cyclophosphamide: 750 mg/m^2 Doxorubicin 50 mg/m^2 Pola: 1.4 or 1.8 mg/kg Q3W		
			Phase II dose expansion R: 375 mg/m^2 Cyclophosphamide: 750 mg/m^2 Doxorubicin: 50 mg/m^2 Pola: 1.8 mg/kg Q3W G: 1,000 mg Cyclophosphamide: 750 mg/m^2	C1D2 0 and 0.5hr, C1D8, C1D15, C2D2, C3D1, C4D1 0 and 0.5hr, TC/ET + PT	

			Doxorubicin: 50 mg/m^2 Pola: 1.8 mg/kg Q3W		

B, bendamustine; C, cycle; CLL, chronic lymphocytic leukemia; D, day; DLBCL, diffuse large B-cell lymphoma; ET, early term; FL, follicular lymphoma; G, obinutuzumab; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; pola, polatuzumab; PT, post-treatment; R, rituximab; R/R, relapsed/refractory; TC, treatment completion; Q3W: every 21 days; Q4W: every 28 days.

[a]Patients in the rituximab-containing arms/cohorts of study GO27834 received up to 17 cycles of treatment and those in the obinutuzumab-containing arms received up to eight cycles. Rituximab was administered on D1 of each 21-day cycle. Pola was administered on D2 of each 21-day cycle; a subset of patients from Arms A–B and Cohort C received rituximab + pola on D1 of every cycle beginning Cycle 3, which follows the same pola sampling schedule as rituximab from Cycle 3. Obinutuzumab was administered on D1, D8, D15 in Cycle 1, then on D1 of each subsequent 21-day cycle.

[b]In the GO29365 study, pola was administered on Day 2 of Cycle 1, and on Day 1 of subsequent cycles, rituximab was administered on D1 of each cycle, or obinutuzumab was administered on D1, D8, D15 in Cycle 1, then D1 of each subsequent cycle. Bendamustine was administered on D2 and D3 in Cycle 1, then D1 and D2 in each subsequent cycle. Patients with FL or DLBCL were administered treatment every 28 or 21 days respectively for six cycles.

[c]In the GO29044 study, patients received up to a total of six (or eight) cycles of treatment. Rituximab, cyclophosphamide, and doxorubicin were administered on D1 of each 21-day cycle; obinutuzumab was administered on D1, D8, D15 in Cycle 1, then D1 of each subsequent 21-day cycle; and pola was administered on D2 of Cycles 1 and 2, followed by D1 of subsequent 21-day cycles.

Table S2 Baseline covariates investigated in the population PK modeling of acMMAE and unconjugated MMAE

Covariate	Model component	Rationale
acMMAE covariates		
Bodyweight	All clearance and volume parameters	Bodyweight influences model parameters for many known drugs
Sex/gender	Clearance, volume	Evaluation of the gender effect is clinically important. Gender may influence clearance and/or volume
Serum albumin	Clearance	It is known that clearance of IgG antibodies is faster in patients with lower serum albumin levels
B-cell count, tumor SPD	Clearance	Target levels may depend on B-cell count and tumor SPD, and may in turn influence clearance
Concomitant therapy, prior therapy	Clearance	Evaluation of the effects of concomitant therapy (rituximab, obinutuzumab) is clinically important
MMAE covariates		
Bodyweight	Clearance, volume	Bodyweight influences model parameters for many known drugs
Sex/gender	Clearance, volume	Evaluation of the gender effect is clinically important. Gender may influence clearance and/or volume
Age	Clearance, volume	Evaluation of the age effect is clinically important
ALT, AST, total bilirubin, hepatic impairment[a]	Clearance	Markers of hepatic function were investigated by diagnostic plots. Hepatic impairment was tested in the model
Disease type and severity (ECOG PS)	Clearance	Target levels may depend on the disease type and severity

Concomitant therapy and prior therapy	Clearance	Evaluation of the effects of concomitant therapy (rituximab, obinutuzumab) is clinically important

All covariates included in the initial full model are shown.

ac, antibody-conjugated; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG, immunoglobulin G; MMAE, monomethyl auristatin E; PK, pharmacokinetics; SPD, sum of product of perpendicular dimensions.

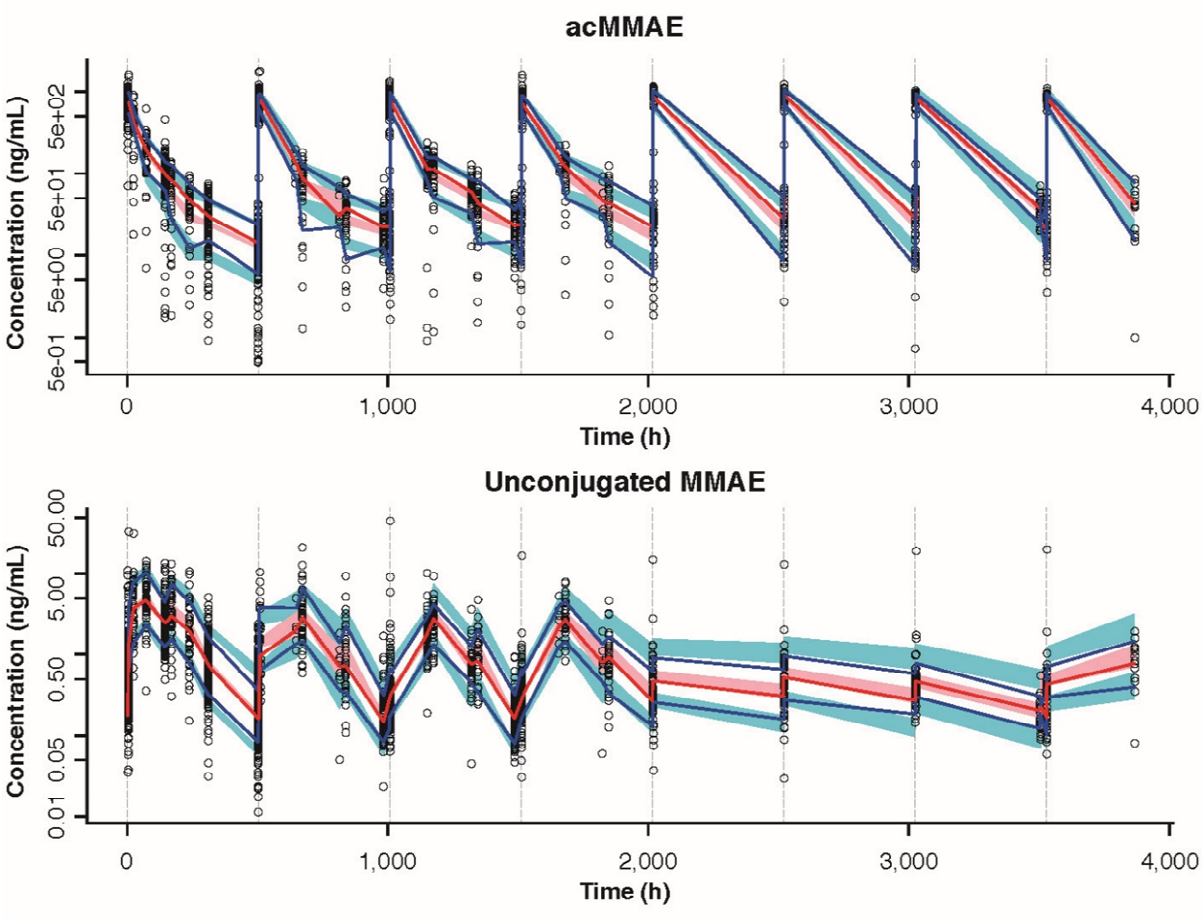
[a]According to National Cancer Institute Organ Dysfunction Working Group criteria.[7]

Table S3 Estimates of random-effects parameters for the final integrated model

Parameter		Description	Value	RSE %	95% CI	CV	Shrinkage %
ω^2_{CLT}	Ω_{11}	Random effect on CL_T	1.89	9.96	1.52–2.26	1.38	17.4
ω^2_{CLINF}	Ω_{22}	Random effect on CL_{INF}	0.0376	6.83	0.0325–0.0426	0.194	8.1
ω^2_{V1}	Ω_{33}	Random effect on V_1	0.0151	9.98	0.0122–0.0181	0.123	11.8
ω^2_{V2}	Ω_{44}	Random effect on V_2	0.107	9.94	0.0859–0.127	0.327	21.6
ω^2_{Q}	Ω_{55}	Random effect on Q	0.0538	13.3	0.0398–0.0678	0.232	30.6
ω^2_{VMAX}	Ω_{66}	Random effect on V_{MAX}	0.462	19.8	0.283–0.641	0.679	33.4
ω^2_{FRACNS}	Ω_{77}	Random effect on conversion fraction	0.0972	9.63	0.0788–0.115	0.312	11.1
ω^2_{CLMMAE}	Ω_{88}	Random effect on CL_{MMAE}	0.115	11.9	0.088–0.141	0.339	21.5
$\omega^2_{V2,MMAE}$	Ω_{99}	Random effect on $V_{2,MMAE}$	0.0422	24.5	0.0219–0.0625	0.205	48.5
$\omega^2_{\sigma acMMAE}$	$\Omega_{10,10}$	Random effect on σ_{acMMAE}	0.0521	9.08	0.0428–0.0614	0.228	–2.7
R $\omega_{\sigma acMMAE}$ $\omega_{\sigma MMAE}$	$\Omega_{11,10}$	σ_{acMMAE} - σ_{MMAE} correlation	0.038	9.32	0.0311–0.045	0.806	–
$\omega^2_{\sigma MMAE}$	$\Omega_{11,11}$	Random effect on σ_{MMAE}	0.0427	12.2	0.0325–0.0529	0.207	0.1
σ^2_{acMMAE}	Σ_{11}	Residual error for acMMAE	0.0254	4.1	0.0233–0.0274	0.159	9.2
σ^2_{MMAE}	Σ_{22}	Residual error for unconjugated MMAE	0.0726	3.86	0.0671–0.0781	0.27	6.4

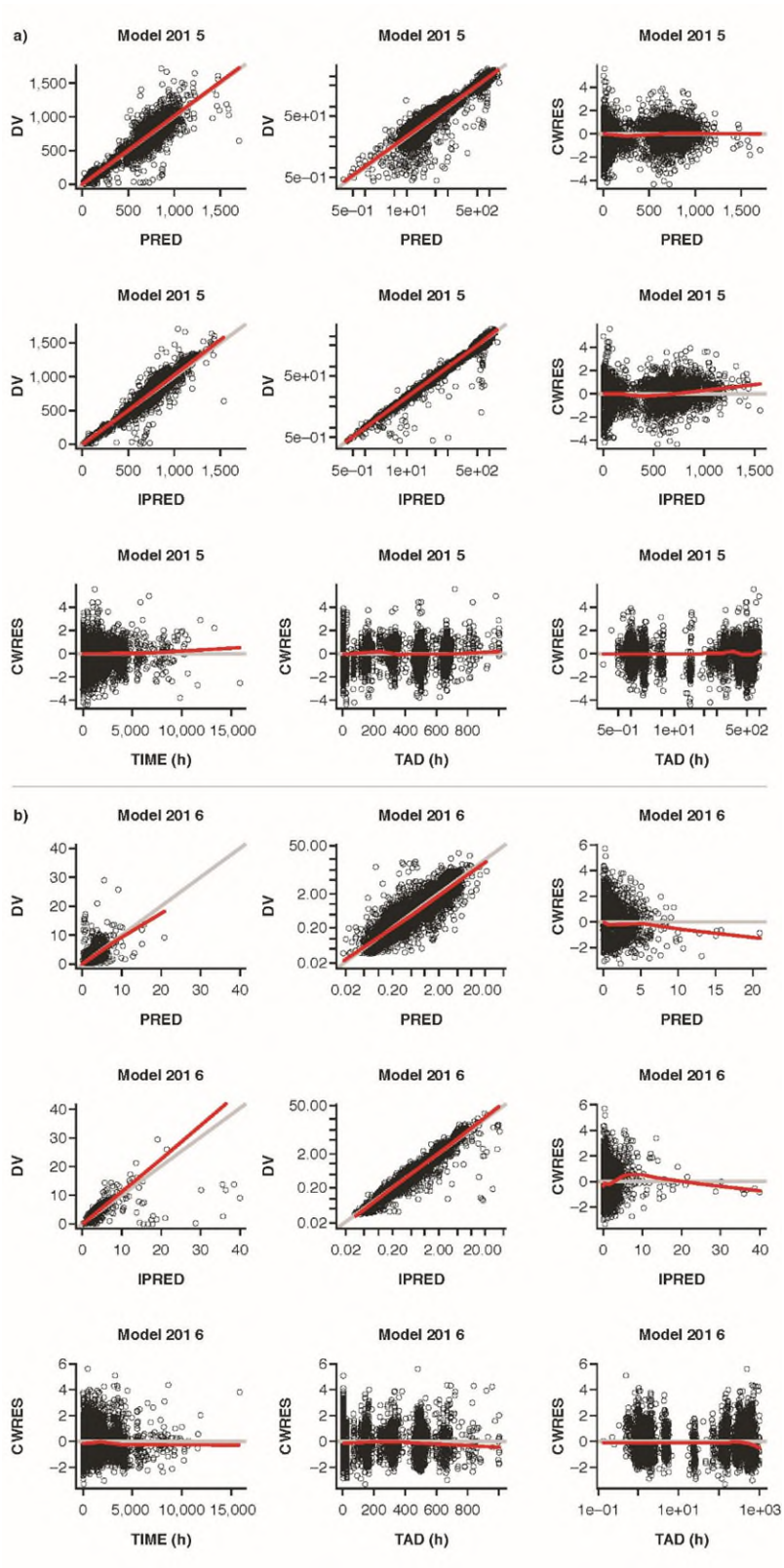
σ^2, variance of residual variability; ω^2, variance of inter-individual variability; ac, antibody-conjugated; CI, confidence interval; CL_{INF}, clearance at infinity; CL_{NS}, non-specific time-dependent linear clearance; CL_t, linear time-dependent exponentially declining clearance; CV, coefficient of variation; MMAE, monomethyl auristatin E; PE, parameter estimate; R, correlation coefficient; RSE (%), relative standard error (i.e., 100·SE/PE); SE, standard error; V_1, central volume; V_2, peripheral volume.

Figure S1. Prediction corrected visual predictive check for Q3W dosing.



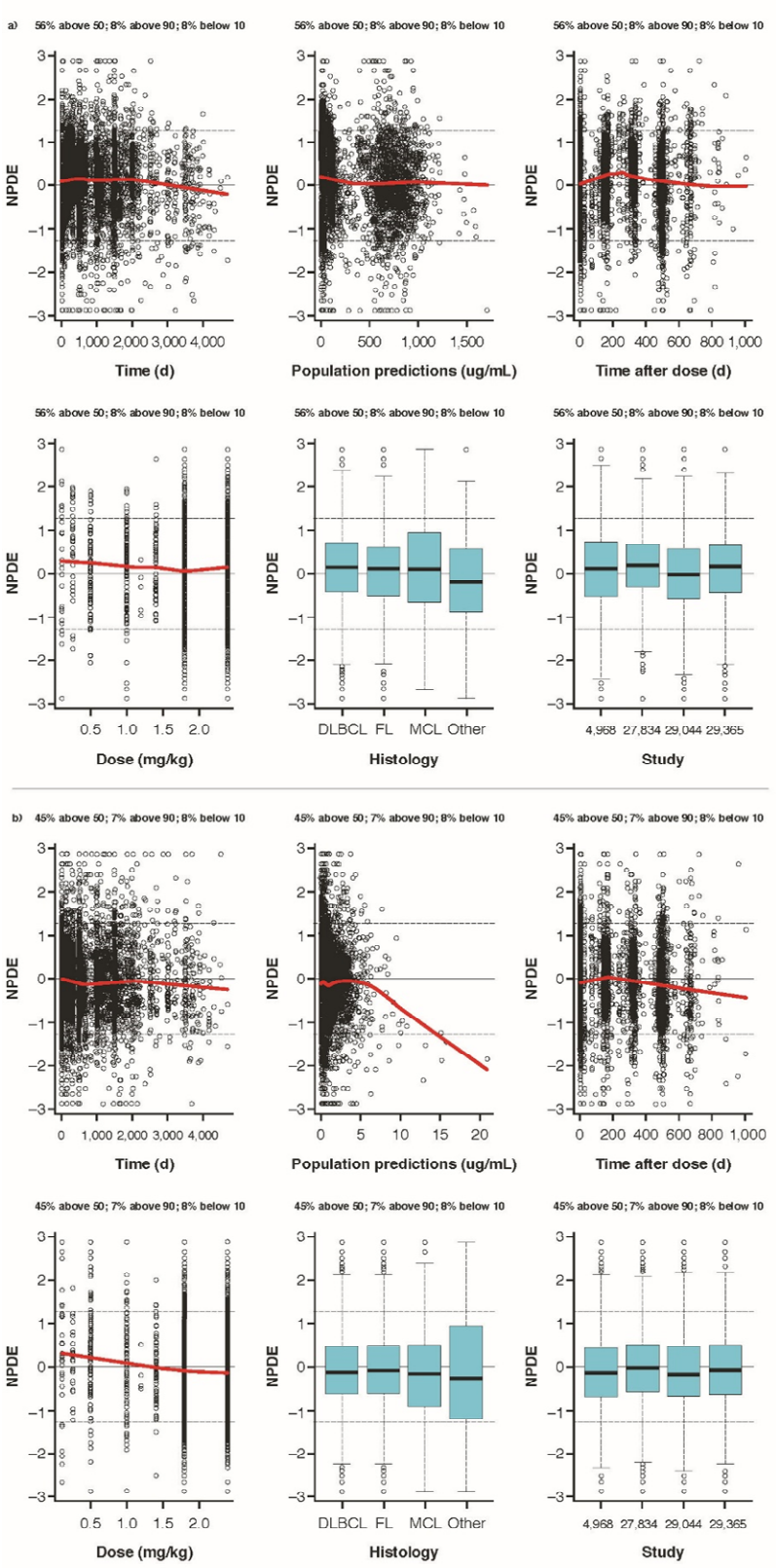
Points are prediction-corrected concentrations. The lines show median (red), and the 10th and 90th percentiles (blue) of the prediction-corrected concentrations. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset. ac, antibody-conjugated; MMAE, monomethyl auristatin E; pc-VPC, prediction-corrected visual predictive check; Q3W, once every 3 weeks.

Figure S2. Goodness-of-fit plots for the integrated model for (**a**) acMMAE and (**b**) unconjugated MMAE.



Gray solid y=x or y=0 lines are included for reference. Bold red lines are the lowess (local regression smoother) trend lines. ac, antibody-conjugated; CWRES, conditional weighted residuals; DV, observed concentrations; IPRED, individual predictions of the model; MMAE, monomethyl auristatin E; PRED, population predictions of the model; TAD, time after the most recent dose; TIME, time after the first dose.

Figure S3 NPDE plots for the integrated model for (**a**) acMMAE and (**b**) unconjugated MMAE.



Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at y=0 correspond to median, and dashed lines show the 10^{th} and 90^{th} percentiles. Percentages of points below the 10^{th} percentile and above the 50^{th} and 90^{th} percentiles are also shown. Red lines show the lowess (local regression smoother) trend lines. ac, antibody-conjugated; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MMAE, monomethyl auristatin E; NPDE, normalized prediction distribution error.

References

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2. Morschhauser, F. et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). *Lancet Haematol.* 6, e254–e265 (2019).

3. Phillips, T. et al. Polatuzumab vedotin combined with obinutuzumab for patients with relapsed or refractory non-Hodgkin lymphoma: preliminary safety and clinical activity of a phase Ib/II study. *Blood.* 128, 622 (2016).

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7. Ramalingam, S.S. et al. Phase I study of vorinostat in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute Organ Dysfunction Working Group study. *J. Clin. Oncol.* 28, 4507–4512 (2010).